Journal of Surgical Oncology 1998;68:209–214

Photodynamic Therapy for Palliation of Chest Wall Recurrence in Patients With Breast Cancer

SCOTT W. TABER, MD,* VICTOR H. FINGAR, PhD, AND T. JEFFERY WIEMAN, MD
Department of Surgery, University of Louisville, Louisville, Kentucky

Background and Objectives: Chest wall recurrence occurs in 5–20% of breast cancer patients. Until recently, the only treatments available were surgical resection or radiotherapy. Photodynamic therapy (PDT) is a new modality that uses a photosensitizer and light to destroy tumor cells selectively. We report here our experience with PDT as a treatment for chest wall recurrence.

Methods: Seven patients with breast cancer who had chest wall recurrence despite previous therapy were treated with PDT. Four patients received one treatment, one received two treatments at the same site, one received two separate treatments at different sites, and one received three separate treatments at distinct sites. Response and adverse events were monitored.

Results: The total response rate of 91% (10/11), with complete response (CR) in 73% (8/11) and partial response (PR) in 18% (2/11), was based on total number of treatments. The mean time to lesion healing was 73 days (range <30–99 days). One patient experienced a photosensitivity reaction after exposure to direct sunlight. No other adverse events were recorded.

Conclusions: PDT is an effective treatment for chest wall recurrence in patients with breast cancer in whom other treatments have failed. PDT is also well tolerated, especially when compared with traditional therapies.

J. Surg. Oncol. 1998;68:209–214.

KEY WORDS: **photodynamic therapy; photochemotherapy; photosensitizer; chest wall recurrence; breast neoplasms; palliative treatment**

INTRODUCTION

Breast cancer is the most common cancer found in women, accounting for approximately 30% of all new cases [1,2]. Although most patients have only local disease and enter remission indefinitely, many develop distant metastases that are associated with discouraging prospects for survival despite intervention [3].

Chest wall recurrence is estimated to occur in approximately 5–20% of breast cancer patients [4–6]. Although rarely the immediate cause of death, chest wall recurrence results in profound physical and psychological morbidity, and often heralds the appearance of other, more life-threatening metastases [7]. If left untreated, the lesions enlarge, spread, ulcerate, and cause a variety of distressing symptoms, including pain, erythema, fungation, foul odor, and bleeding [8–12]. These symptoms not only necessitate continuous medical attention, but can affect the patient's self-image; create personal, social, and financial losses; and are constant reminders of the presence of disease [8,13].

Traditionally the two most common treatments for chest wall recurrence have been site-specific radiation and chest wall resection. Radiation therapy typically produces complete response rates (total disappearance of tumor) of approximately 65% [9,14]. However, there are many side effects associated with radiation therapy in-

*Correspondence to: Scott W. Taber, MD, University of Louisville, Department of Surgery, Norton Hospital Cancer Treatment Center, Alliant Medical Pavillion, 315 East Broadway, Louisville, KY 40202. Fax No.: 502-629-3183. E-mail: swtabe01@pdt.louisville.edu

Accepted 13 May 1998

cluding systemic symptoms of nausea and vomiting; local symptoms of erythema, pruritus, and flaking of skin at the site of therapy [15]; and, in rare cases, the induction of new neoplasms [16]. Surgical therapy involves removal of the affected tissue, and is effective only for the treatment of discrete lesions. Although surgical excision is associated with an initial high rate of complete response, approximately 75% of patients will have a re-recurrence of chest wall disease [11,14]. In addition, surgical chest wall resection has the same risks and complications associated with any major surgical procedure, and follow-up care is extensive [15]. Finally, cosmetic disfigurement may be severe with either treatment, depending on the extent of disease and the size of the treated area [17]. Systemic treatments, such as chemotherapy and hormone therapy, are used less frequently and are generally less effective at controlling chest wall lesions [14].

Photodynamic therapy (PDT), an emerging alternative to radiation therapy and surgical resection, involves administration of a photosensitizing agent followed by nonthermal monophasic laser light. This combination leads to the generation of free radicals and singlet oxygen, which are directly cytotoxic, and also results in tumor death via ischemic necrosis secondary to vascular occlusion [18,19]. Although the photosensitizing agent is taken up by all tissues, it is selectively retained primarily by tumor cells and tumor vasculature [20,21]. The enhanced retention by tumor tissue, along with the precise application of light, accounts for the selective killing of cancer cells while sparing the surrounding normal tissue.

PDT is currently marketed in the United States for the palliation of esophageal cancer. Investigations have shown, however, that PDT is effective in a variety of tumor types, including skin, endobronchial, bladder, head and neck, and chest wall recurrences [10,21–26]. PDT has been well tolerated in patients treated for these tumors, especially compared with other methods of treatment, and is a relatively noninvasive procedure that requires little pre- and post-treatment care. The only clinically significant adverse event, observed in all patients treated with PDT, is dermal photosensitivity, usually for up to 1 month after treatment [10]. This can be easily managed by having patients avoid exposure to direct sunlight or bright indoor light. Necrosis of the treated area was also observed, but this effect was limited to the tumor-infiltrated tissue and healed with few sequelae [26].

The need for additional treatment options that yield equal or greater efficacy with more favorable adverse event profiles motivated our investigations of PDT for chest wall recurrence. Previous results documenting the use of PDT for this indication have shown overall response rates of approximately 65% [10,25,26]. The results reported herein represent our preliminary clinical experience with PDT for the treatment of chest wall recurrence in seven patients with breast cancer.

PATIENTS AND METHODS

Patients

From March 1996 to December 1997, seven patients with chest wall recurrence originating from primary breast cancer were enrolled. All patients had previously received other therapies for both the primary and recurrent malignancies, and had a chest wall recurrence despite these treatments or were unable to tolerate therapy. Patients were required to be more than 18 years of age, and of nonchildbearing potential (postmenopausal, permanently sterilized, or practicing a medically acceptable form of contraception). Patients must not have received any radiation therapy or chemotherapy containing a doxorubicin-like compound within 2 weeks before the start of this study. Informed consent was obtained from all patients, and approval was granted by the Institutional Review Board of the University of Louisville.

Treatment

The photosensitizing agent, porfimer sodium (Photofrin® QLT Phototherapeutics, Inc., Vancouver, BC), was supplied as a freeze-dried powder and reconstituted with 5% dextrose, resulting in a final concentration of 2.5 mg/ml. Patients received 1–2 mg/kg body weight of porfimer sodium, administered intravenously over a 10-min period through either a central venous catheter or a vein in the arm. The line was then flushed with 5% dextrose solution.

Light was administered to the chest wall 48 h after porfimer sodium injection, allowing for maximum drug retention in the tumor and maximum drug clearance from noninvolved tissues [10,25]. The light was administered through an argon-pumped dye laser tuned to 630-nm wavelength (Coherent, Santa Clara, CA). The laser light dosage was 25–100 J/cm^2 of tissue, with a light intensity of 7–150 mW/cm^2. If ulcerated lesions developed at the treatment site, local wound care was initiated with topical antibiotics (e.g., silver sulfadiazine; polymyxin creams) and simple gauze dressings. Pain medication was administered at the physician's discretion.

Patient Monitoring

Blood pressure, pulse rate, and oxygen saturation were monitored every 15 min for one hour posttreatment. All patients were then monitored within 48–72 h after light exposure and were instructed to call the hospital if they experienced adverse effects. Patients were re-evaluated within 1 week after treatment, weekly for 1 month, and then every 2 weeks until the treated lesions were healed, as determined by re-epithelialization of the tumor site and no palpable tumor nodules, or death. A complete response (CR) was defined as the elimination of all vis-

TABLE I. Photodynamic Therapy for Chest Wall Recurrence in 7 Patients: Baseline Characteristics of the Study Population by Patient*

Patient	Age (yr) at diagnosis	Stage of primary disease	Time to chest wall recurrence	Site of other metastasis	Karnofsky score	Previous treatments	
						Irradiation (cGY)	Other (including chemotherapy)
1	79	IIIB	10 mo	Negative	⩾80	4,600–5,000	MRM/vinorelbine/tamoxifen/ mitoxantrone/cyclophosphamide
2	73	IIIB	19 mo	Bone	⩾80	4,500	Mastectomy/axillary node dissection/tamoxifen/methotrexate/ 5-FU
3	65	IV inflammatory	11 mo	Lung	⩾70	6,500	Cyclophosphamide/doxorubicin/5-FU/ paclitaxel
4	47	IIIB	62 mo	Negative	⩾90	⩾6,100	MRM/cyclophosphamide/doxorubicin/ hyperthermia/BMT
5	28	IIIB	51 mo	Supraclavicular lymph nodes	⩾90	1,000–5,000	Cyclophosphamide/methotrexate/5-FU/ doxorubicin/paclitaxel/platinum/BMT
6	69	II	14 mo	Negative	⩾90	None	Chest wall resection
7	59	II	14 yr	Negative	⩾90	5,000	Cytotoxin/Adriamycin/placed on tamoxifen

*BMT, bone marrow transplant; 5-FU, 5-fluorouracil; MRM, modified radical mastectomy.

ible tumor from the treatment site; a partial response (PR) was defined as a flattening of the tumor nodule or partial necrosis.

RESULTS

Patients

A total of seven women with chest wall recurrence secondary to breast cancer completed treatment, with four treated once, one treated twice at the same site, one who received two separate treatments at different sites, and one who received three separate treatments at different sites. Table I lists the baseline characteristics for this population. All patients had advanced cancer and were heavily pretreated with irradiation and/or a variety of chemotherapy regimens, including paclitaxel, vinorelbine tartrate, cyclophosphamide, and 5-fluorouracil (5-FU). Three patients had a mastectomy, and two patients received prior bone marrow transplants (BMT) for primary disease. Duration of breast cancer averaged 6 years (range <1–14 years) before the initiation of PDT. Four deaths were attributable to other metastases unrelated to chest wall recurrence. Three patients are currently alive, are free of chest wall disease, and have Karnofsky performance scores of >80%.

Response

All patients experienced a response to PDT (Table II). Of the 11 treatments administered, eight (73%) resulted in a CR and two (18%) resulted in a PR, for a total response rate of 91% (10/11); one patient was unevalu-

TABLE II. Photodynamic Therapy for 11 Chest Wall Recurrences in 7 Patients: Response Data*

Patient	Area of PDT (cm^2)	Length of treatment	Response	Time to lesion healing	Follow-up
1	173		PR	58 days	Decreased; lesions flattened with no palpable disease
2	59	50 min	CR	<30 days	Alive with no evidence of chest wall disease
3	191	3 h, 47 min	NA	death <30 days	Deceased; symptomatic with itching and ulcerated lesions, but no visible tumor nodules
4[a]	423	1 h, 53 min	CR	84 days	—
4	920	9 h, 20 min over 2 days	CR	84 days	—
4	455	6 h	CR	84 days	Deceased with no evidence of chest wall disease
5	260	2 h, 33 min	CR	[b]	Deceased with no evidence of chest wall disease
6	169	1 h, 35 min	PR	99 days	—
6	199	2 h, 39 min	CR	[b]	Alive with no evidence of chest wall disease
7	151	1 h, 54 min	CR	30 days	Alive with chest wall disease outside the area treated with surgery plus PDT
7[c]	78.5	42 min	CR	Healing	Alive with tumor outside of the area treated with PDT

*CR, complete response; PR, partial response; NA, not available; PDT, photodynamic therapy.
[a]Patient No. 4 was treated three separate times at different sites.
[b]Not completely healed at last evaluation.
[c]Patient No. 7 was treated two separate times at different sites.

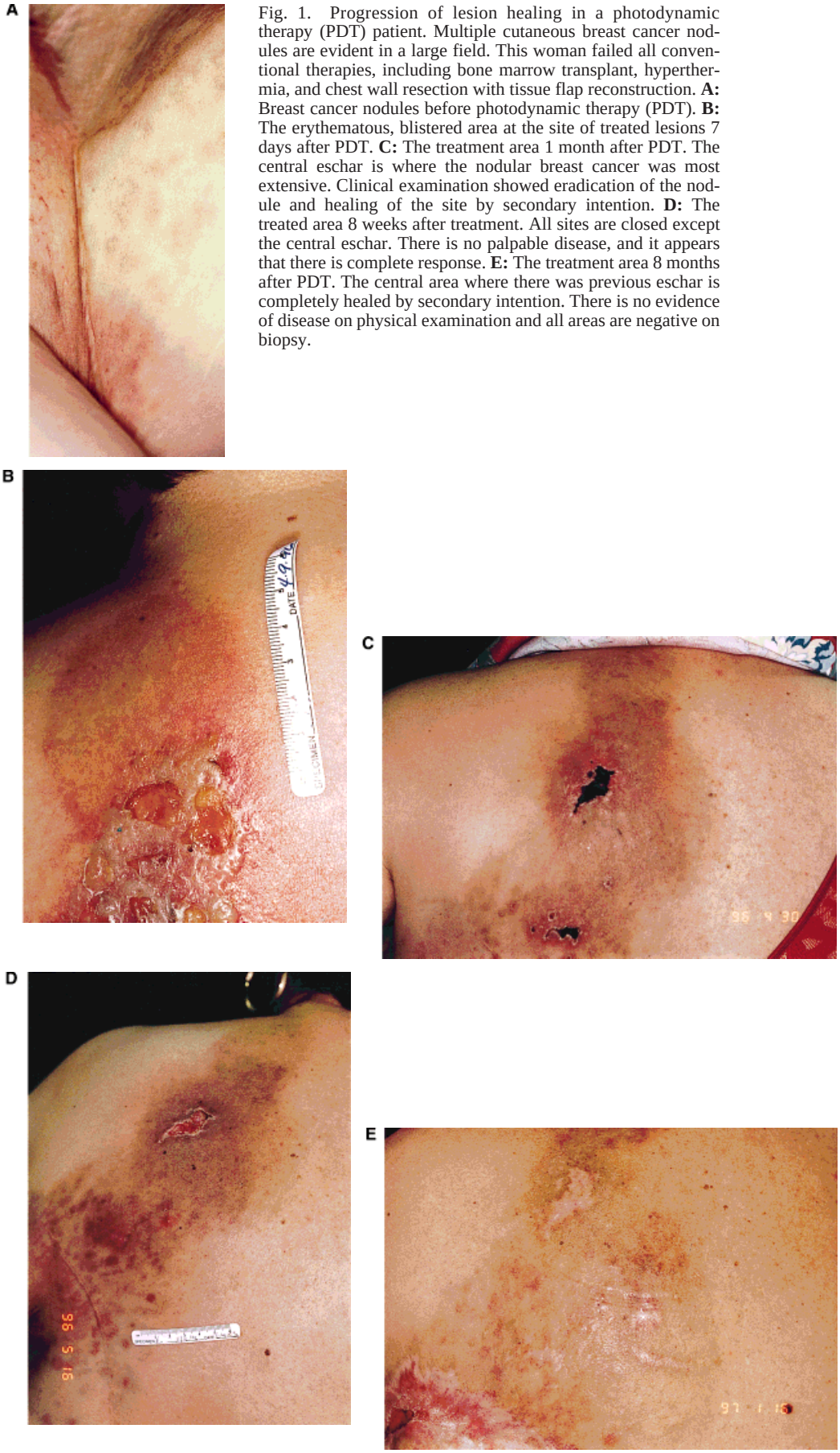

Fig. 1. Progression of lesion healing in a photodynamic therapy (PDT) patient. Multiple cutaneous breast cancer nodules are evident in a large field. This woman failed all conventional therapies, including bone marrow transplant, hyperthermia, and chest wall resection with tissue flap reconstruction. **A:** Breast cancer nodules before photodynamic therapy (PDT). **B:** The erythematous, blistered area at the site of treated lesions 7 days after PDT. **C:** The treatment area 1 month after PDT. The central eschar is where the nodular breast cancer was most extensive. Clinical examination showed eradication of the nodule and healing of the site by secondary intention. **D:** The treated area 8 weeks after treatment. All sites are closed except the central eschar. There is no palpable disease, and it appears that there is complete response. **E:** The treatment area 8 months after PDT. The central area where there was previous eschar is completely healed by secondary intention. There is no evidence of disease on physical examination and all areas are negative on biopsy.

able due to death <30 days after therapy. The CR rates within the treatment sites resulted from dosage administration of 100 J/cm^2, while PR rates occurred with doses of <100 J/cm^2. The mean time to lesion healing was 73 days (range <30–99 days).

The first follow-up visit was 7 days after treatment, and was continued monthly until the patient's death; three patients continue to be monitored. Only two patients, including the patient who succumbed within 1 month of treatment, had any evidence of chest wall disease at the time of death. Lesions healed as predicted (Fig. 1); at the time of light application there was erythema, which was not specific to the treated area. At 7 days, an eschar was present and the tumor was ulcerated, with preservation of the normal skin. The eschar had either lifted or was debrided in the office at 1 month after treatment, and there was clinical evidence of granulation tissue with re-epithelialization from the periphery of the normal epithelium.

Safety

PDT was well tolerated. Wounds were easily managed in the outpatient setting. The only adverse event observed during the length of the study, experienced by only one patient, was a mild skin toxicity after extended exposure to the sun.

DISCUSSION

This study reports the results of PDT in seven patients with chest wall recurrence after treatment of primary breast cancer. All patients had advanced disease, for which they received extensive therapy, including mastectomy, BMT, radiation therapy, and chemotherapy. All but three are deceased, which is not unexpected, given the clinical course of metastatic breast cancer for patients with advanced disease [2].

Previous reports have shown that PDT is effective in treating breast cancer which is locally recurrent to the chest wall. An early study observed a CR in 7% (2/30) of patients, and a PR in 73% (22/30) of patients treated with PDT, with a duration of response varying from 6 weeks to 8 months [25]. In a later study, PDT resulted in 20% (4/20) of patients experiencing a CR, and 45% (9/20) experiencing a PR, with an average duration of 2.5 months [26]. A third study evaluating PDT in 37 patients reported a CR rate of 13.5% and a PR rate of 35.1% [10].

Our results show a 91% (10/11) total response rate, 73% (8/11) CR, and 18% (2/11) PR, considerably higher than those previously reported, which may be attributable to improved technology or to the small number of patients treated. It is important to note that we observed a response in heavily pretreated patients who had received prior therapy both for the original cancer and for chest wall disease. These patients are historically difficult to treat and often do not find relief for chest wall recurrence from conventional approaches [14]. Response did not correlate with length of treatment but was influenced by stage of disease and time to recurrence from original diagnosis. Patients with more aggressive disease had more extensive previous therapy, had a shorter time between diagnosis and chest wall recurrence, and were less likely to experience a CR from PDT.

There were few side effects associated with PDT in this study, and lesions healed with few sequelae. As expected, time to lesion healing correlated with size of the treated area: the larger the treatment area, the longer the time to heal. One patient was exposed to the sun for an extended period of time and experienced dermal photosensitivity at the exposed areas. No other adverse events were reported. The low incidence of PDT-related adverse events in this study is supported by previous work on head and neck, lung, and skin cancers [21,22,27].

The apparent lack of side effects associated with PDT is especially important when considering the breast cancer patient's quality of life. Other treatment modalities, such as surgery and radiotherapy, produce significant side effects that have a profound impact on patient well being. A high standard of quality of life in patients is not only associated with patient comfort, but may affect survival. A study of patients with advanced breast cancer found a significant correlation between high quality-of-life scores and increased survival [28]. In addition, this association was maintained when other prognostic factors, including tumor response, were taken into consideration. Thus, additional benefit may be attained by treating chest wall lesions with the least invasive procedure possible, such as PDT, so as to improve quality of life and possibly increase disease-free survival.

CONCLUSIONS

Chest wall recurrence is associated with significant morbidity and patient anxiety. Not only are the lesions painful and unsightly, but they are also a reminder that the patient is not free from visible disease despite previous, and often debilitating, procedures. PDT, a relatively new option for patients who experience chest wall recurrence, involves administration of a photoreactive drug followed by laser light directed at the particular target area. Our results suggest that PDT relieves patients of the disabling symptoms of chest wall disease, and is a noninvasive procedure that is highly tolerable, especially when compared with alternative modalities.

REFERENCES

1. Parker SL, Tong T, Bolden S, Wingo PA: Cancer statistics, 1997. CA Cancer J Clin 1997;47:5–27.
2. Phillips DM, Balducci L. Current management of breast cancer. Am Fam Physician 1996;53:657–665.
3. Clark G, Sledge G, Osborne CK, McGuire WL: Survival from first recurrence: Relative importance of prognostic factors in 1015 breast cancer patients. J Clin Oncol 1987;5:55–56.

4. Nordman DE, Linna NM, Nieminen S: Local recurrence of breast carcinoma after mastectomy and radiotherapy. Strahlentherapie 1977;153:13–16.
5. Ottesen G, Andersen JA, Blichert-Toft M, Axelsson C: Frequency and types of chest wall recurrences among node negative breast cancer patients. Acta Oncol 1988;27:601–604.
6. Rissanen PM: A comparison of conservative and radical surgery combined with radiotherapy in the treatment of stage I carcinoma of the breast. Br J Radiol 1969;42:423–426.
7. Gilliland MD, Barton RM, Copeland EM: The implications of local recurrence of breast cancer as the first site of therapeutic failure. Ann Surg 1983;197:284–287.
8. Bedwinek JM, Fineberg B, Lee J, Ocwieza M: Analysis of failures following local treatment of isolated local-regional recurrence of breast cancer. Int J Radiat Oncol Biol Phys 1981;7:581–585.
9. Chu FC, Lin F-J, Kim JH, et al.: Locally recurrent carcinoma of the breast. Cancer 1976;37:2677–2681.
10. Khan SA, Dougherty TJ, Mang TS: An evaluation of photodynamic therapy in the management of cutaneous metastases of breast cancer. Eur J Cancer 1993;29A:1686–1690.
11. Miyauchi K, Koyama H, Noguchi S, et al.: Surgical treatment for chest wall recurrence of breast cancer. Eur J Cancer 1992;28A: 1059–1062.
12. Shah JP, Urban JA: Full thickness chest wall resection for recurrent breast carcinoma involving the bony chest wall. Cancer 1975; 35:567–573.
13. McDonald AE: Skin ulceration. In Groenwald SL, Frogge MH, Goodman M, Yarbro CH (eds): ''Cancer Symptom Management.'' Boston: Jones and Bartlett, 1997:364–376.
14. Beck TM, Hart NE, Woodard DA, Smith CE: Local or regionally recurrent carcinoma of the breast; results of therapy in 121 patients. J Clin Oncol 1983;1:400–405.
15. Yarbro CH: Principles of Oncology Nursing. In Holland JF, Bast RC Jr, Morton DL, Frei E III, Kufe DW, Weichselbaum RR (eds): ''Cancer Medicine.'' 4th Ed. Baltimore: Williams & Wilkins, 1997:1351–1356.
16. Fisher B, Osborne CK, Margolese RG, Bloomer WD: Neoplasms of the breast. In Holland JF, Bast RC Jr, Morton DL, Frei E III, Kufe DW, Weichselbaum RR (eds): ''Cancer Medicine.'' 4th Ed. Baltimore: Williams & Wilkins, 1997:2400.
17. Pierce LJ, Lippman M, Ben-Baruch N, et al.: The effect of systemic therapy on local-regional control in locally advanced breast cancer. Int J Radiat Oncol Biol Phys 1992;23:949–960.
18. Henderson BW, Waldow SM, Mang TS, et al.: Tumor destruction and kinetics of tumor cell death in two experimental mouse tumors following photodynamic therapy. Cancer Res 1985;45:572–576.
19. Weishaupt KR, Gomer CJ, Dougherty TJ: Identification of singlet oxygen as the cytotoxic agent in photo-inactivation of a murine tumor. Cancer Res 1976;36:2326–2329.
20. Dougherty TJ: Hematoporphyrin derivative for detection and treatment of cancer. J Surg Oncol 1980;15:209–210.
21. Wilson BD, Mang TS, Stoll H, et al.: Photodynamic therapy for the treatment of basal cell carcinoma. Arch Dermatol 1992;128: 1597–1601.
22. Biel MA: Photodynamic therapy and the treatment of head and neck cancers. Semin Surg Oncol 1995;11:355–359.
23. Kato H, Okunaka T, Shimatani H: Photodynamic therapy for early stage bronchogenic carcinoma. J Clin Laser Med Surg 1996;14: 235–238.
24. Nseyo UO: Photodynamic therapy in the management of bladder cancer. J Clin Laser Med Surg 1996;14:271–280.
25. Schuh M, Nseyo UO, Potter WR, et al.: Photodynamic therapy for palliation of locally recurrent breast carcinoma. J Clin Oncol 1987;5:1766–1770.
26. Sperduto PW, DeLaney TF, Thomas G, et al.: Photodynamic therapy for chest wall recurrence in breast cancer. Int J Radiat Oncol Biol Phys 1991;21:441–446.
27. Furuse K, Fukuoka M, Kato H, et al.: A prospective phase II study on photodynamic therapy with Photofrin II for centrally located early-stage lung cancer. J Clin Oncol 1993;11:1852–1857.
28. Coates A, Gebski V, Signorini D, et al.: Prognostic value of quality-of-life scores during chemotherapy for advanced breast cancer. J Clin Oncol 1992;10:1833–1838.